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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,266	12/20/2006	Sabine Gack	085449-0188	3606

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,266	GACK ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/11/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed May 11, 2009, is acknowledged.

2. Claims 65-72 are pending and under examination as they read on a method for the diagnosis of a disease selected from the group consisting of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, and gestational diabetes, comprising determining the expression level of a peptide or polypeptide ADAM- 12 and the species of preeclampsia and PIGF.

3. Applicant's IDS, filed 5/11/09, is acknowledged.

4. The following new ground of rejections are necessitated by the amendment submitted 5/11/09.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 65-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 65 and 69 are incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination. In the instant case, no contacting step is recited in the claims.

B) In claims 65 and 69 (b(ii)), the recitation "any of the amino acid sequences according to i) of at least 95% over 100 amino acid residues" lacks sufficient antecedent basis in base claim 65(i) and 69(i). There is only one sequence in 65(i) and 69(i), no multiple sequences can be found in claims.

Applicant's arguments, filed 5/11/09, have been fully considered, but have not been found convincing.

Applicant submits that the additional step of contacting the sample with the necessary reagents as suggested by the Examiner is unnecessary. Applicant submits that the step of determining the amount of a marker inherently requires such a contacting step.

It is the Examiner's position that the contacting step is required to determine the amount of a maker in the sample. Without the contacting step the skilled in the art would not know how to determine the amount of a marker in the sample.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 65-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the diagnosis of preeclampsia comprising (a) obtaining a serum or plasma sample from a pregnant women in the late 2nd and early 3rd trimester, (b) contacting samples from pregnant women with anti-ADAM 12-S (SEQ ID NO:4) antibodies and (c) compare the level of ADAM 12-S in said serum sample to a gestational age-matched serum obtained form healthy women, wherein an increase in ADAM 12-S level in the serum is indicative of preeclampsia, does not reasonably provide enablement for a method for the diagnosis of preeclampsia or diagnosing a pregnant woman at increased risk of eclampsia, pregnancy induced hypertension, HELLP syndrome and intrauterine growth retardation, comprising

a) obtaining any "sample" from the pregnant woman in the 2nd or 3rd trimester of pregnancy,

b) "determining the amount" of a protein having an amino acid sequence as presented in SEQ ID NO: 4, or a protein "having" any "amino acid sequence exhibiting a sequence identity with any of the amino acid sequences according to at least 95% over 100 amino acid residues", c) comparing the determined amount of the marker with a reference amount derived from getration age matched healthy women; and d) establishing a diagnosing based on the result of step c), wherein a higher determined amount of the marker as compared to the reference amount of the marker is indicative of preeclampsia or is indicative of an increased risk of at least one of eclampsia, pregnancy induced hypertension, HELLP syndrom and intrauterine growth retardation.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

There is not nexus between the level of ADAM 12-S and a woman at increased risk of eclampsia, pregnancy induced hypertension, HELLP syndrome and intrauterine growth retardation. It is not clear whether pregnancy induced hypertension, HELLP syndrome and intrauterine growth retardation are caused by or result from preeclampsia. For example, preeclampsia usually developed in primigravidas or women with preexistent vascular disease such as hypertension. It is known that significantly higher baseline blood pressure observed in as early as 9-12 weeks of gestation in women who subsequently become preeclamptic. Accordingly, it is not clear whether pregnancy induced hypertension is a causative factor or a

consequence of the development of preeclampsia.

The claimed invention is directed to diagnosis of preeclampsia and a related disease comprising determining the level of ADAM 12-S or fragments thereof, an amino acid sequence exhibiting 95% sequence identity over 100 amino acid residues of ADAM 12 or a fragment thereof of which is at least 100 amino acids in length.

Christiansen et al (Prenat Diagn 27, 611-615., 2007) teach that ADAM 12 as a second-trimester maternal serum marker in screening for Down syndrome. Accordingly, it is not clear whether an increase in ADAM12-s in the second trimester would indicate preeclampsia or Down syndrome.

The specification discloses that the 68 kDa protease was easily detected in the sera of both groups (preeclamptic patients and gestational age-matched healthy), however, it was significantly increased in the serum of patients diagnosed with preeclampsia (FIG. 3) (see page 51, lines 2-4). Wewer et al in JBC 281(14)9418-9422, 2006, teaches that Western blot analysis or pregnancy serum using antibodies to the cysteine-rich domain of ADAM12 revealed a 68-kDa single band. To further test whether the prodomain is also present, human pregnancy serum was analyzed by western blot using a mixture of antibodies to the prodomain and to the cysteine-rich domain. Wewer et al found that a 25 kDa prodomain to the present in pregnancy serum but not in non-pregnancy serum (see page 9419, under Results and Discussion). Accordingly, the presence of a protein having an amino acid sequence exhibiting a 95% sequence identity with 100 amino acid residues of SEQ ID NO: 4, is not indicative of any disease and does not lead to diagnosis of preeclampsia or the risk of diseases associated with preeclampsia, but rather indicate indicates the woman is pregnant. Applicant fails to provide a correlation between an increase in the 25kDa prodomain in a pregnant woman and preeclampsia. No significant increase in the serum level of the 25kDa fragment or any other Adam12 fragments were show in the preeclampsia patients.

Also, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases and recognized that it was unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

Besides ADAM 12-S (secreted), the specification fails show that ADAM 12-L or any ADAM 12

fragment is present in the sera from either preeclampsia or control even though the specification uses polyclonal antibodies that would detect the ADAM 12-L or any ADAM 12 fragment. It is known in the art that ADAM 12-L is a membrane-bound protein, and the skilled in the art would not expect to see the membrane-bound ADAM 12-L in any body fluid including sera. The specification fails to show any correlation between the ADAM 12-L or ADAM 12 fragment and any disease including preeclampsia. Yet, Applicant is claiming a method for the diagnosis of preeclampsia using any ADAM 12 fragment and any sample. While the specification uses polyclonal antibodies to detect ADAM 12-S, Figure 3 show not other bands that would qualify as 95% identical to claimed ADAM 12 polypeptides. Yet, Applicant claims determining the expression level of a peptide or polypeptide with a sequence comprising 95% identity with ADAM 12 or fragments thereof.

Also at issue the measurement of expression of any of the genes listed in claims 67, 68, 71 and 72 in serum or plasma samples. It is not clear how gene expression can be measured in a serum sample or plasma sample.

Finally, it is not clear how to determine the amount of the marker in the sample. Besides using anti-ADAM12-s antibodies, the specification fails to provide guidance on how to determine the amount of a marker in the sample.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention

Applicant's arguments, filed 5/11/09, have been fully considered, but have not been found convincing.

Regarding sampling, Applicant argue that increased expression levels of ADAM 22S RNA are shown in preeclamptic placental tissue as compared to control placental tissue in figures 1 and 2.

This is not found persuasive because the elected invention is drawn to a protein not a nucleic acid. A sample that can be use to determine the protein is not the same as the sample that can be use to determine the nucleic acid. Accordingly, Applicant's argument is irrelevant to the elected invention.

9. Claims 65-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "a protein having an amino acid sequence exhibiting a sequence identity with any of the amino acid sequences [presented in SEQ ID NO: 4] (according to i)) of at least 95% over 100 amino acid residues" as part of the invention.

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, the 95% sequence identity fragments SEQ ID NO: 4 and it's preeclampsia marker function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of peptide or polypeptide having any amino acid exhibiting a sequence identity with SEQ ID NO: 4 of at least 95% over 100 amino acid residues, which retain the features essential to the instant invention.

Applicant has disclosed only increase in amino acid of SEQ ID NO: 4 level in the sera for patients diagnosed with preeclampsia; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 15, 2009

/Maher M. Haddad/
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